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(21) International Application Number: PCT/EP95/04334 (22) International Filing Date: 4 November 1995 (04.11.95) (30) Priority Data: 08/339,428 14 November 1994 (14.11.94) US (71) Applicant: ZYMA S.A. [CH/CH]; Route de l'Etraz, CH-1260 Nyon (CH). (72) Inventors: BRAUN, Richard, Louis; 3 Tory Court, Colts Neck, NJ 07722 (US). CAROSELLI, Robert; 5 Independence Drive, East Brunswick, NJ 08816 (US). CLEMENTE, Theodore, Jr.; 65 Michelle Lane, Belle Mead, NJ 08502 (US). SANDBECK, Sandra, Ervy; Apartment 14A, 7 Green Street, Metuchen, NJ 08840 (US). (74) Agent: HILLEBRAND, Dirk; Ciba-Geigy AG, Patentabteilung, Klybeckstrasse 141, CH-4002 Basle (CH).		(81) Designated States: AL, AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG). Published <i>With international search report.</i>
(54) Title: USE OF MENTHYL LACTATE AS A PAIN RELIEVER (57) Abstract The use of menthyl lactate for the manufacture of a topical composition for achieving topical pain relief is disclosed. Furthermore, the invention concerns a method of achieving topical pain relief which method comprises topically applying to the external skin of a mammal including man a topical pain relieving effective amount of menthyl lactate.		

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Use Of Menthyl Lactate As A Pain Reliever

Field Of The Invention

The invention relates to the field of analgesics and in particular to topical analgesics. The invention further relates to the field of menthol esters.

Background Of The Invention

Menthol has been used in various topical preparations as a counterirritant, as an aesthetic agent (for its fragrance), and as a plasticizer in denture adhesive compositions. Unfortunately, the aroma of menthol has been a significant hinderance to its use in any meaningful amount other than where its fragrance is desired.

In compositions containing effective counter-irritant amounts of menthol (1.25% to 16% according to the FDA monograph for menthol), the aroma from menthol can be overpowering.

Various menthol esters have been prepared. Most of these esters have disagreeable odors, making them truly unsuitable for use in a topical product. These odors are as disagreeable as, or more so than, menthol itself, especially in amounts which are equimolar with monograph counter-irritant effective amounts of menthol.

Menthyl lactate is a known compound available e.g. from Haarmann & Reimer GmbH (Germany) under the name FRESCOLAT, Type ML. Two thirds of its molecular weight is attributable to the menthol moiety. The manufacturer's product literature indicates that it is a "cooling agent" and that it can be used in body care and cosmetic products in which "long lasting cooling and freshness are desired". According to the manufacturer, menthyl lactate is virtually odorless, not suffering from the "mint note" that is otherwise customary in the case of other menthol derivatives. The compound is recommended for use as a flavor in concentrations of 0.005% to 0.2% and in cosmetic and other external products in concentrations ranging from 0.2% to 2.0%. The maximum recommended amount of menthyl lactate as per the product literature is therefore 2.0% by weight, which would correspond

1.3% by weight of the menthol moiety. Nowhere is there any indication or suggestion that menthyl lactate should be used as a topical pain reliever or at concentrations substantially in excess of those indicated by the product literature.

Objects Of The Invention

An object of the invention is to provide a topical pain reliever for external treatment.

Another object of the invention is to provide a substantially odor-free composition having topical analgesic properties.

Summary Of The Invention

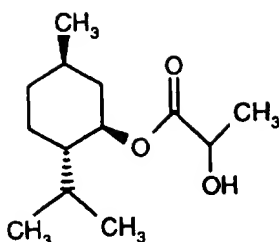
These and other objects of the invention can be achieved by using menthol lactate as the topical pain relieving active agent.

Detailed Description Of The Invention

The invention concerns a method of achieving topical (= external) pain relief, in an animal in need thereof comprising the application of a topical or mucous membrane suitable composition to the skin of said animal, wherein said composition comprises a topical or mucous membrane pain relieving effective amount of menthyl lactate. "Animal" preferably means warm-blooded animal (= mammal) and includes man.

Moreover, the invention relates to the use of menthyl lactate (for the manufacture of a topical composition) for achieving topical pain relief. The topical composition may either be a pharmaceutical one or a veterinary one, preferably a pharmaceutical one. The topical composition is preferably applied to the skin or a mucous membrane of the subject to be treated.

Menthyl lactate is the lactate ester of menthol and has the structural formula



(I).

The compound is available commercially under the name FRESCOLAT, Type ML from Haarmann & Reimer GmbH (Germany). It can also be readily made by processes known in the art by esterifying the hydroxy group of menthol with lactic acid.

For use as a topical pain reliever, menthyl lactate is present in compositions compatible with this use in amounts which range from about 2.0% to about 22% by weight of the total composition, preferably about 6.0% to about 18%, more preferably about 9.0% to about 15%, by weight of the total composition. The remainder of the composition may be any suitable topical carrier which is compatible with menthyl lactate.

The external topical preparations of the invention can be applied to any portion of the skin. However, application to the external genitalia, or the eyelids, or lips is not suggested, recommended, or usually desired.

Typical external topical carriers and additives suitable for use in the present invention include, but are not limited to, carriers such as lanolin, white petrolatum, propylene glycol (preferably up to about 10%, more preferably about 2% to about 8%), paraffin, an alcohol selected from ethanol and isopropyl alcohol (preferably up to about 30%, more preferably about 10% to about 25%), and water (preferably up to about 80%, more preferably about 45% to about 75%); surfactants such as TWEEN (preferably TWEEN 80) (preferably up to about 2.2%, more preferably about 0.2% to about 2.0%), and glyceryl stearate; thickeners such as accacia, methylcellulose, tragacanth, or a carbomer (preferably carbomer 980 or carbomer 940) (preferably up to about 1.5%, more preferably about 0.5% to about 1.2%);

pH adjusters such as triethanolamine (preferably up to 2.4%, more preferably about 0.5% to about 2.0%);

and fragrance (preferably up to about 5.5%, more preferably about 0.2% to about 5.0%, most preferably about 0.5% to about 4.0%), especially eucalyptus oil (preferably up to 5.5%, more preferably about 0.2% to about 5.0%), and the like, and mixtures thereof.

The compositions for use in the present invention may take any appropriate form for the intended application area including, but not limited to, solutions, suspensions, powders, creams, ointments, impregnated bandages, etc.

The present invention formulations are applied generally as needed anywhere from once to 6 or more times a day, depending on the degree of relief required and the nature of the pain involved. The patient can suitably self regulate the frequency with which the compositions need be applied.

The following example is intended to exemplify, but not to limit the invention.

Example 1:

<u>Ingredient</u>	<u>Amount</u>
Carbomer 980	0.8%
Purified Water	67.2%
Propylene Glycol	5.0%
Menthyl Lactate	9.0%
Eucalyptus Oil	0.5%
SD 3A Alcohol (= ca. 95 Vol% ethanol denatured with ca. 5 Vol% methanol)	15.0%
TWEEN 80	0.5%
Triethanolamine	1.0%
Fragrance	1.0%

The Carbomer 980 is dispersed in approximately 90-99% of the water in a mixing tank. The propylene glycol is then added to the dispersion. In a separate tank, mix together and

- 5 -

dissolve the alcohol, TWEEN 80, fragrance, eucalyptus oil, and menthyl lactate. The second mixture is then added to the first mixture with continued mixing. In a third tank, the triethanolamine is dissolved in the remaining water. The third mixture is then added to the first mixing tank with continued mixing.

What is claimed is:

1. The use of menthyl lactate for the manufacture of a topical composition for achieving topical pain relief.
2. The use according to claim 1 wherein the menthyl lactate is incorporated into the topical composition in a concentration of from about 2.0% to about 22% by weight of the total composition.
3. The use according to claim 1 wherein the menthyl lactate is incorporated into the topical composition in a concentration of from about 6.0% to about 18% by weight of the total composition.
4. The use according to claim 1 wherein the menthyl lactate is incorporated into the topical composition in a concentration of from about 9.0% to about 15% by weight of the total composition.
5. A method of achieving topical pain relief in an animal in need thereof comprising topically applying to the external skin of said animal a topical pain relieving effective amount of menthyl lactate.
6. The method of claim 5 wherein said menthyl lactate is applied in a concentration of from about 2.0% to about 22% by weight of the total composition.
7. The method of claim 5 wherein said menthyl lactate is applied in a concentration of from about 6.0% to about 18% by weight of the total composition.
8. The method of claim 5 wherein said menthyl lactate is applied in a concentration of from about 9.0% to about 15% by weight of the total composition.
9. A topical pharmaceutical composition for achieving topical pain relief consisting essentially of menthyl lactate and at least one topically acceptable carrier.

10. Menthyl lactate for use as a topical pain reliever.

INTERNATIONAL SEARCH REPORT

International Application No

PC1/EP 95/04334

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	AGRIC BIOL CHEM, 43 (2). 1979. 307-312., SAKATA I ET AL 'SYNTHESIS AND PROPERTIES OF MENTHYL GLYCOSIDES' see the whole document ---	1-10
X	DE,A,26 08 226 (HAARMANN & REIMER GMBH) 8 September 1977	9,10
A	see the whole document -----	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

20 February 1996

Date of mailing of the international search report

01.03.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Mair, J

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 95/04334

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 5-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound. (Rule 39.1 (1v) PCT).
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 95/04334

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A-2608226	08-09-77	FR-A- 2342057	23-09-77
		JP-A- 52105223	03-09-77
		NL-A- 7702074	30-08-77